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Datasheet for the decision of 4 October 2022

Case Number: T 0073/20 - 3.3.07

Application Number: 12836127.6

Publication Number: 2761296

IPC: G01N33/533, C07D207/40

Language of the proceedings: EN

Title of invention:
RAPID FLUORESCENCE TAGGING OF GLYCANS AND OTHER BIOMOLECULES WITH ENHANCED MS SIGNALS

Patent Proprietor:
Waters Technologies Corporation

Opponent:
Dörner, Eva

Headword:
Procainamide succinimidylcarbamate/WATERS

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 12(6), 13(2)

Keyword:

Inventive step - obvious solution
Amendment to case - reasons for submitting amendment in appeal proceedings (no)
Amendment after summons - exceptional circumstances (no)

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Case Number: T 0073/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 4 October 2022

Appellant: (Patent Proprietor)	Waters Technologies Corporation a US Corporation 34 Maple Street Milford, MA 01757 (US)
Representative:	Forresters IP LLP Skygarden Erika-Mann-Straße 11 80636 München (DE)
Respondent: (Opponent)	Dörner, Eva Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Representative:	Dörner, Eva Charlotte Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 October 2019 revoking European patent No. 2761296 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

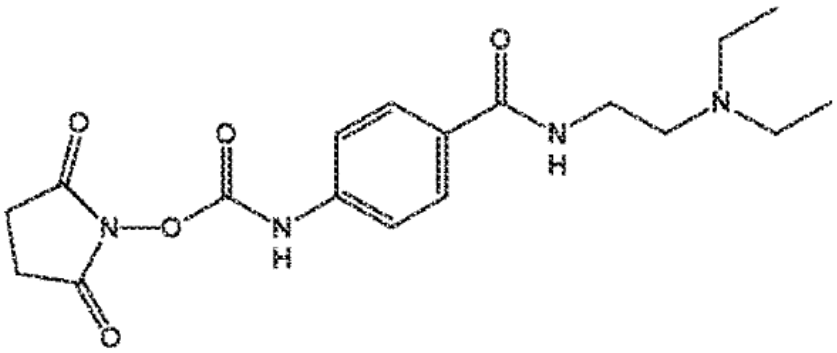
Chairman	A. Usuelli
Members:	J. Molina de Alba
	L. Bühler

Summary of Facts and Submissions

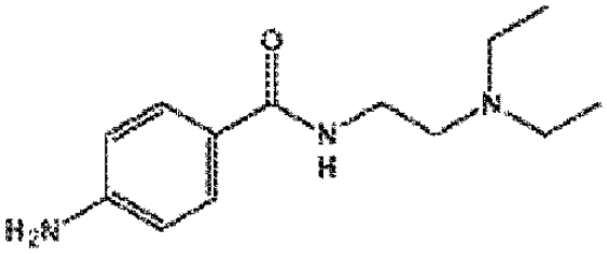
I. This appeal by the patent proprietor (appellant) is directed against the opposition division's decision revoking European patent No. 2 761 296.

II. The patent had been granted with two claims. Granted claim 1 reads as follows:

"*1. A compound of the structural formula*"



This compound is a derivative of procainamide, the compound cited in paragraph [0091] of the patent and in D1, which has the following formula:



III. The patent was opposed on the ground of Article 100(a) EPC for lack of inventive step.

IV. The documents cited during the opposition proceedings included the following:

D1: S. Klapoetke et al., Journal of Pharmaceutical and Biomedical Analysis, 53(2010), 315-24
D2: WO 2009/100155

V. In the decision under appeal, the opposition division concluded that the claimed subject-matter was obvious over a combination of document D1 with document D2.

VI. The appellant filed an appeal requesting that the decision be set aside and that the patent be maintained as granted (main and sole request).

VII. In its reply to the statement of grounds of appeal, the respondent (opponent) requested that the appeal be dismissed.

VIII. The board scheduled oral proceedings in line with the parties' requests and gave its preliminary opinion.

IX. In response to the board's preliminary opinion, the appellant filed the following document:

D7: J. Yan et al., "Comparison of Common Fluorescent Labels for LC/MS Analysis of Released N-Linked Glycans", Application Note Pharma&Biopharma, Agilent Technologies, Inc., 2019

X. Oral proceedings were held before the board on 4 October 2022. At the end of the oral proceedings, the board announced its decision.

XI. The appellant's arguments relevant to the present decision can be summarised as follows.

The argument that the skilled person had a technical prejudice against the application of the teaching of D2 to the compound of D1 should be admitted. The compound resulting from that combination of documents had a urea linking group, so the skilled person would expect it to produce a lower MS signal. This expectation relied on the common general knowledge that the delocalisation of the electronic density on the nitrogen atom of the urea group impaired ionisation. This was not a new argument but a development of the argument submitted in the reply to the notice of opposition (page 6, paragraph below the title "Technical effect") that D2 did not contain any disclosure or explanation on the MS signal of its compounds. Furthermore, the argument was based on the teaching in the patent (paragraphs [0037] and [0062]) that the rapid labelling agents in the prior art did not link to the glycan via an amino group and that this resulted in a reduction of the MS signal.

Document D7 should be admitted into the appeal proceedings as a reaction to the board's preliminary opinion. On page 3, last sentence, the board indicated that the appellant's argument that the urea linking group impaired fluorescence or MS signals was not supported. This issue had never been raised before. So there were exceptional circumstances justifying the filing of D7, which contains experimental evidence supporting the appellant's position on this matter.

The compound of claim 1 was inventive starting from D1 as the closest prior art. D1 taught the use of procainamide as a labelling agent for profiling and

identifying glycans by fluorescence and MS. The compound of claim 1 differed from procainamide in the succinimidyl carbamate moiety. This difference allowed a faster labelling of glycans. Therefore, the objective technical problem was improving the speed of glycan labelling.

The compound of claim 1 was not an obvious solution to this problem. The skilled person would not have derivatised procainamide with the succinimidyl carbamate moiety suggested in D2 for several reasons. First, the authors of D1 did not consider that the speed of glycan labelling was problematic, so the skilled person had no motivation for seeking a faster method of labelling. Second, D1 did not contain any prompt to turn to D2. Third, the teaching of D2 was incompatible with that of D1; D1 aimed to provide both a strong fluorescence and a strong MS signal, whereas D2 cared only for a strong fluorescence signal. Fourth, the skilled person had no expectation of success that linking procainamide to the glycan via a urea group, as would result from the method of D2, would preserve the good MS signal of procainamide. The same could happen with the fluorescence signal. This was corroborated by the post-filing evidence in Appendixes A and B (filed during the examination proceedings with the letter dated 21 June 2016) and in D7.

XII. The respondent's arguments relevant to the present decision can be summarised as follows.

The appellant's argument that there was a technical prejudice in the prior art against combining the teaching of D1 and D2 because a reduction of the MS signal could be expected should not be admitted. The argument was raised in the statement of grounds of

appeal for the first time. Contrary to the appellant's contention, page 6 (section "Technical effect") of the reply to the notice of appeal did not refer to any teaching in D2 involving a technical prejudice. As to paragraph [0037] of the patent, it referred to 2-aminobenzamide and rapid labelling agents available in the prior art but not to procainamide, this representing the disclosure of the closest prior art. In any case, even with paragraph [0037] in the patent, the appellant never argued in the opposition proceedings that there was a technical prejudice against the use of labelling agents resulting in urea linking groups.

Document D7 should not be admitted into the appeal proceedings either. This document did not belong to the prior art, so it was unsuitable for addressing the board's objection in its preliminary opinion (page 3, last sentence) that there was no evidence of a technical prejudice in the prior art against the combination of D1 and D2. Furthermore, this objection had already been raised by the respondent in its reply to the appeal (page 15, paragraph 72, third and fourth sentences), but the respondent did not react until the board mentioned it in its preliminary opinion.

D1 was the closest prior art; it was directed to the labelling of glycans with procainamide for their profiling and identification via fluorescence and MS. The use of procainamide provided an equivalent fluorescence signal and highly improved ionisation efficiency with respect to the reference compound 2-aminobenzamide. Moreover, minimal structural and functional modification was required to arrive at the procainamide derivative of claim 1.

The compound of claim 1 differed from procainamide in the succinimidyl carbamate moiety. This difference enabled a faster labelling of glycans. Therefore, the objective technical problem was the provision of an activated form of procainamide that allowed a more rapid labelling of glycans.

In view of D2, the compound of claim 1 was an obvious solution to this problem. Even if D1 did not consider the labelling speed to be a problem, the skilled person's motivation arose from the objective technical problem. D2 also provided a motivation because it aimed to reduce the long incubation times and elevated temperatures needed when, as in D1, glycans were labelled with amino compounds by reductive amination. Procainamide was encompassed by the amino compounds that could be modified according to D2 (Formula Id-1 on page 13 and paragraph [0046]). The aim of D2 was achieved by adding an activating group to the labelling agent, namely a succinimidyl carbamate group. The teaching of D2 was not incompatible with that of D1; D2 not only disclosed the profiling of glycans by fluorescence, it also used MS for identification. Contrary to the appellant's view, the skilled person would not expect the urea link between the glycan and the labelling agent added by the method of D2 to impair the MS signal of procainamide. The same was true for the alleged potential loss of the fluorescence signal.

XIII. The parties' final requests were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main and sole request).

It also requested that document D7, filed with the letter dated 27 April 2022, be admitted into the proceedings.

- The respondent requested that the appeal be dismissed. She further requested that document D7, filed with the letter dated 27 April 2022, as well as the appellant's arguments relating to a prejudice in the art regarding the urea linking group, not be admitted into the appeal proceedings.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Admittance of a new argument in appeal proceedings

2.1 In the statement of grounds of appeal (paragraphs 24 and 44 to 53), the appellant argued that there was a technical prejudice in the prior art against the combination of the teaching of D1 and D2. The skilled person would have derived from D1 that it was essential for good MS and fluorescence signals that the group linking the labelling agent to the glycan be an amino group. As the linking group resulting from the method of D2 was a urea, the skilled person would have expected a loss of the MS signal and possibly also of the fluorescence signal when the method was used on the compounds of D1. According to the appellant, this prejudice was based on the skilled person's common general knowledge that a urea linking group would impair ionisation efficiency because the electronic

density on the nitrogen atom of the urea group would be delocalised and centred on the oxygen atom.

The appellant submitted that this argument was not new; it was just a development of the arguments put forward in the opposition proceedings (reply to the notice of opposition, page 6, section "Technical effect") and was based on the teaching in paragraphs [0037] and [0065] of the patent (see also appellant's letter dated 27 April 2022, section "Introduction-inventive step").

2.2 The respondent requested that the argument not be admitted into the appeal proceedings. As the statement of grounds of appeal was filed after entry into force of the RPBA 2020, the relevant provision for the admittance of the new argument is Article 12(4) and (6) RPBA 2020 (see also Article 25 RPBA 2020).

2.3 In accordance with Article 12(2) RPBA 2020, to which Article 12(4) refers, a party's appeal case must be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based. The decision under appeal did not mention at any point the argument that there was a technical prejudice in the prior art deterring the skilled person from combining the teaching of D1 and D2. Nor did the decision refer to a principle in the prior art that the delocalisation of the electronic density on the nitrogen atom of a urea group would impair the MS signal of a compound.

In accordance with Article 12(4) RPBA 2020, first paragraph, the above argument is an amendment to the appellant's case unless the appellant demonstrates that the argument was admissibly raised and maintained in the proceedings leading to the decision under appeal.

On this point, the appellant referred to the section "Technical effect" on page 6 of its reply to the notice of opposition. That section explains that D2 does not deal with the issue of the MS signal. However, it is silent on any technical prejudice in the prior art supported by the skilled person's common general knowledge. The argument could also not be found in the section "Obviousness" bridging pages 6 and 7 of the reply to the opposition. There, the appellant argued that the skilled person had no motivation to combine D1 with D2, not that there was a prejudice against that combination of documents. Therefore, the new argument is an amendment to the appellant's case and may be admitted only at the discretion of the board.

Article 12(4) RPBA 2020, second sentence establishes the appellant's obligation to identify any amendment to its case and provide reasons for submitting it in the appeal proceedings. On the admittance of the amendment, Article 12(4) RPBA 2020, third paragraph provides that the board must exercise its discretion in view of, *inter alia*, the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal and the need for procedural economy. Furthermore, Article 12(6) RPBA 2020, second paragraph rules that the board must not admit requests, facts, objections or evidence which should have been submitted in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

The appellant failed to fulfil its obligation under Article 12(4) RPBA 2020, second paragraph. It neither identified the amendment to its case nor provided reasons for submitting it in the appeal proceedings. Furthermore, no circumstances justify the filing of the

new argument in the appeal proceedings. The argument could and should have been filed in the opposition proceedings since the facts on which it relies were known to the appellant from the outset of the opposition proceedings. This is confirmed by paragraph [0037] of the patent, which hints at a relationship between the electron density on amino and urea groups and their corresponding MS signals. However, the appellant did not raise this issue during the opposition proceedings and brought it up for the first time in appeal.

As this submission could not be justified as a legitimate reaction to late developments in the opposition proceedings and created a new situation on appeal, the board exercised its discretion not to admit the new argument under Article 12(4) and (6) RPBA 2020.

3. Admittance of D7

Document D7 was filed by the appellant in response to the board's preliminary opinion in preparation for the oral proceedings. Its admittance is to be assessed under Article 13(2) RPBA 2020, which provides that any amendment to a party's appeal case made after notification of the summons to oral proceedings is, in principle, not to be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned.

According to the appellant, D7 contains post-filing experimental evidence responding to the board's view in the last sentence on page 3 of its preliminary opinion. That sentence indicated that the appellant's contention that the urea linking group could potentially impair the fluorescence or MS signals was unsupported.

Therefore, in the appellant's view, there were exceptional circumstances justifying the admittance of D7 into the appeal proceedings.

The board disagrees. The last sentence on page 3 of the board's preliminary opinion is in the context of the board's preliminary assessment of the appellant's new submission on appeal. The board pointed to the lack of evidence for the alleged technical prejudice in the prior art, and noted that post-filed experimental evidence could not be seen to reflect the skilled person's mindset at the relevant date. These indications did not raise any new issues; they merely pointed to the fact that the appellant's new submission was not supported by suitable evidence, as required by Article 12(3) RPBA 2020 (see also Article 12(5) RPBA 2020). A party cannot shift its responsibility under this provision to the board and wait for a negative opinion to complete its case. Furthermore, it is apparent that the submission of additional post-filing evidence was unsuitable for addressing the board's concern. Therefore, there were no exceptional circumstances justifying the filing of D7, and the board decided not to admit it pursuant to Article 13(2) RPBA 2020.

4. Inventive step

4.1 The patent (paragraphs [0001] to [0003]) is concerned with the labelling of glycans for their profiling and identification using fluorescence and MS techniques. It explains that existing labelling agents give a good fluorescence signal but that they either react very slowly or give a poor MS signal. So the patent seeks compounds that allow a fast labelling reaction and at the same time provide good fluorescence and MS signals.

4.2 The respondent considered that document D1, cited in paragraph [0045] of the patent, was the closest prior art. At the oral proceedings before the board, the appellant did not contest that D1 was a suitable springboard.

Like the patent, D1 (abstract) is directed to the labelling of glycans for their profiling and identification using fluorescence and MS (ESI-QTOF) detection. D1 teaches that labelling glycans with procainamide through reductive amination improves fluorescence detection and ESI ionisation efficiency, i.e. MS signal. In its experimental part, D1 (page 316, right-hand column, second full paragraph) describes the labelling of a sample with procainamide by reductive amination, a process that requires heating at 65 °C for 3 hours. The authors of D1 (page 324, right-hand column, first paragraph) observed that the labelled glycan generated a fluorescence signal comparable to that of the reference labelling compound 2-aminobenzamide and that its ionisation efficiency was improved by 10 to 50 fold.

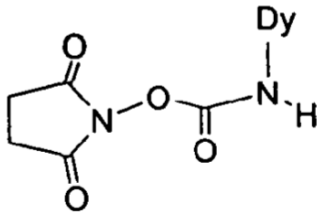
4.3 It was common ground between the parties that the compound of claim 1 differed from procainamide in its succinimidyl carbamate moiety and that this difference enabled a faster labelling of glycans. In addition, it was undisputed that the glycans labelled with the compound of claim 1 give good fluorescence and MS signals. These effects are demonstrated in Example III of the patent, which shows that glycans can be labelled with the compound of claim 1 in five minutes at room temperature and that they can be analysed by fluorescence and MS detection.

4.4 The objective technical problem can therefore be formulated as the provision of a compound which enables a faster labelling of glycans while maintaining a good level of fluorescence and MS signals.

4.5 The respondent did not contest that this problem was solved by the compound of claim 1. Neither does the board, especially in view of Example III of the patent.

4.6 However, the board holds that the compound of claim 1 was an obvious solution in light of D2.

4.6.1 D2 (abstract; paragraph [0005]) discloses a rapid method for labelling glycans with a fluorescent tag under mild conditions. The method relies on the use of a fluorescent amine functionalised with a succinimidyl carbamate group as the labelling agent (paragraphs [0071] to [0073] and Scheme 2). The functionalised fluorescent amine has the following generic formula in which Dy is a fluorescent dye:



This formula encompasses the compound of claim 1: according to the embodiment of Formula Id-1 on paragraph [0055] of D2, Dy is (p-phenyl)R^2, in which R^2 may be $C(O)NR^aR^b$ (page 10, lines 30 and 32) and R^aR^b may be H and an alkyl group substituted with a di(C_{1-8}alkyl)amino group (page 11, lines 5, 6, 15 and 16).

Compared with labelling through reductive amination, which requires typical incubation times of two to three

hours, labelling with carbamates according to D2 is completed within minutes (page 26, lines 3 to 5).

Therefore, the skilled person wishing to increase the speed of glycan labelling with procainamide in D1 was prompted to functionalise procainamide with the succinimidyl carbamate group proposed in D2. There is no disclosure in D1 or D2 suggesting that this modification of procainamide could result in an impairment of the fluorescence or MS signals of the labelled glycans (see also the penultimate paragraph in point 4.6.2 below). Hence, the skilled person would have arrived at the compound of claim 1 in an obvious manner.

4.6.2 The appellant argued that the skilled person would not have combined D1 with D2 for four reasons:

(i) The authors of D1 did not consider the speed of labelling to be a problem, so the skilled person had no motivation to improve it.

(ii) There was no pointer in D1 for the skilled person to turn to D2.

(iii) The teaching of D2 was incompatible with D1 because D2 did not care about the MS signal; only fluorescence was considered important.

(iv) The skilled person could not have expectations of success because the electron-withdrawing nature of the urea linking group suggested in D2 would have

impaired the fluorescence and MS signals of procainamide.

Regarding (i), the skilled person did not need to find motivation in D1 for increasing the speed of glycan labelling. This motivation was provided by the objective technical problem as formulated above (point 4.4) in view of the technical effect provided by the distinguishing feature.

Regarding (ii), the skilled person did not need a pointer in D1 to turn to D2. Once again, the motivation to turn to D2 comes from the skilled person's intention to solve the objective technical problem to enable a faster labelling of glycans while maintaining a good level of fluorescence and MS signals. This intention prompted the skilled person to look for information on how to label glycans faster.

Regarding (iii), there is no incompatibility between the teaching of D1 and D2. On the one hand, D1 does not teach that the good fluorescence and MS signals of procainamide are attributable to the amino linking group or that this group should not be modified. On the other hand, the fact that D2 focuses on fluorescence does not mean that its method would be detrimental to the MS signal of procainamide or that the obtained glycans could not be identified by MS; no passage in D2 suggests a detrimental effect on the MS signal of the labelled glycans. In fact, D2 (paragraph [0082]) contemplates the possibility of analysing labelled glycans by MS, as done in Example 13.

Regarding (iv), this is the argument that the board did not admit under Article 12(4) and (6) RPBA 2020 (see point 2 above). Although this time the appellant did

not refer to a technical prejudice in the prior art but to a lack of expectation of success by the skilled person, the argument is the same. It relies on the same alleged facts and has the same purpose: in view of common general knowledge, the skilled person would expect the urea linking group resulting from the method of D2 to impair ionisation efficiency due to a delocalisation of the electronic density on the nitrogen atom towards the oxygen atom. In fact, the only passage in the statement of grounds of appeal in which the appellant mentioned a lack of expectation of success was in paragraph 44. This paragraph referred to the alleged technical prejudice against a combination of D1 and D2. Therefore, the board did not take this argument into consideration.

4.7 It follows that the compound of claim 1 as granted lacks an inventive step, contrary to Article 56 EPC, and that the ground for opposition of Article 100(a) EPC precludes the maintenance of the patent as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated